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THE UNITED STATES OF AMERICA

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APPLICATION NUMBER: ***60/556,754***
FILING DATE: ***March 26, 2004***

EP 05/3186

By Authority of the
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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22987 U.S.PTO 60/556754

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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 10 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☐ Other (specify)

☑ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

☑ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-1182

☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE Amount ($): $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

[Page 1 of 2]

Respectfully submitted,

SIGNATURE

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Date March 26, 2004

REGISTRATION NO. 40,879 *(if appropriate)*

Docket Number: M602

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Docket Number M602

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Number 2 of 2

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APPLICATION DATA SHEET

APPLICATION INFORMATION

Application Type:	Provisional
Subject Matter:	Utility
CD-ROM:	None
Computer Readable Form:	No
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Attorney Docket No.:	M602
Request For Early Publication:	No
Request For non-Publication:	No
Total Drawing Sheets:	None
Small Entity?:	Yes

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DOMESTIC PRIORITY INFORMATION

Application	Continuity Type	Parent Application	Parent Filing Date

FOREIGN PRIORITY INFORMATION

Country	Application No.	Filing Date	Priority Claimed

ASSIGNEE INFORMATION

Assignee Name:

NANOPARTICLE FORMULATIONS OF PLATINUM COMPOUNDS

The present invention concerns solid lipid nanoparticles of platinum compounds of therapeutic interest.

BACKGROUND OF THE INVENTION

Solid lipid nanoparticles or microparticles (SLNs or SLMs) or nanospheres are lipid particles having an average diameter smaller than one micron and usually in the range from some hundreds to a few nanometers, which have been thoroughly studied as carriers for controlled drug delivery. SLNs may be prepared by a number of methods from solid lipids, including e.g. high pressure homogenization (EP 605497) and via microemulsions (US 5,250,236).

Reviews of the preparation as well as of the pharmaceutical applications of SLNs are reported for instance in Eur. J. Pharmaceutics and Biopharmaceutics, 50 (2000), 161-177, and in Pharm. Technol. Eur. 13 (2001) 32-42.

Pharmaceutical compositions in form of SLMs suitable for parenteral administration of drugs are particularly disclosed in EP 988031. Said formulations are characterized by specific compounds such as fatty acids, PEG-stearate, dipalmitoylphosphatidylethanolamine-PEG and the like, which stabilize said microparticles avoiding phagocytosis.

Microparticles particularly suited for drug delivery across mucosal tissues and the blood-brain barrier are disclosed in WO 99/27918 and US 6,419,949. A number of medicaments including antibiotics, hormones and antitumor agents of different kinds are specifically cited.

Platinum compounds are among the most effective anticancer drugs used to treat solid tumors. After intravenous administration, platinum species tend to bind irreversibly to plasma proteins (covalent binding) in a time dependent kinetic, with more than 90% drug bound within a few hours from administration. Furthermore, for some new platinum complexes the fraction of drug that is free in plasma water and that reversibly

bound to plasma protein seems to undergo a progressive and rapid degradation to form inactive de-platinated species. These species are likely to be generated because of platinum compound chemical instability in plasma, possibly due to the interaction with nucleophilic thiol-containing endogenous molecules (e.g. cysteine residues, glutathione). The high degree of plasma protein binding in humans probably favors such interaction. Both the high irreversible binding to plasma protein and the fast degradation in human plasma may hamper platinum compounds efficacy in clinical trials.

DESCRIPTION OF THE INVENTION

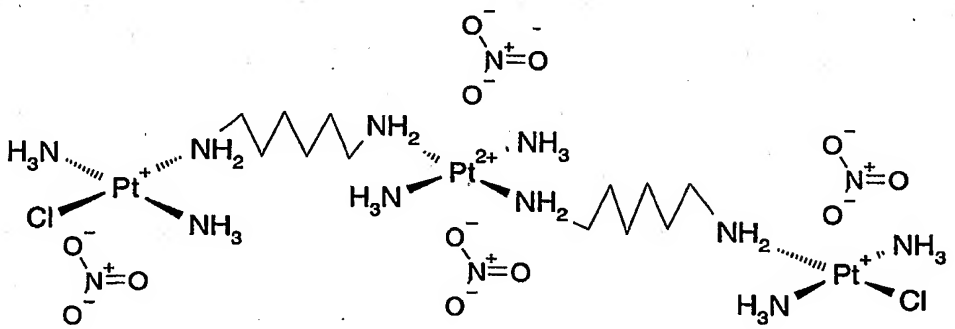
It has now been found that platinum compounds having antitumor activity can be advantageously formulated into SLNs or SLMs, surprisingly improving the therapeutic index thereof.

According to the present invention, preferred platinum compounds include platinum complexes wherein the platinum metal atom is chelated by suitable ligands, particularly anionic ligands and ligands containing amino groups.

Preferred compounds are described in US 6,022,892, US 6,060,616, US 5,744,497, US 6,011,166, and US 6,596,889.

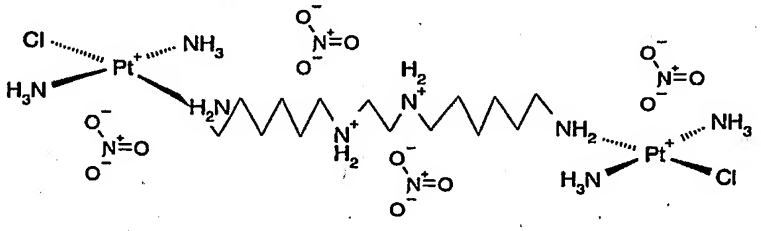
Particularly preferred compounds are:

trans-{bis[trans(diammine)(chloro)platinum (II)(μ-1,6-hexanediamine)]}diammineplatinum tetranitrate salt of formula I, described in the Example 6 of US 5,744,497:



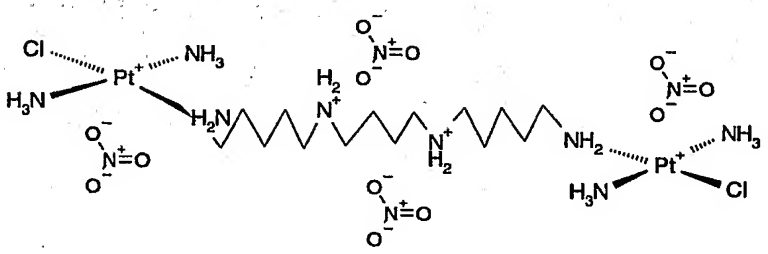
Formula 1

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-7,10-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3 of formula II, described in Example 17, page 15, line 25-31 of US 6,022,892:



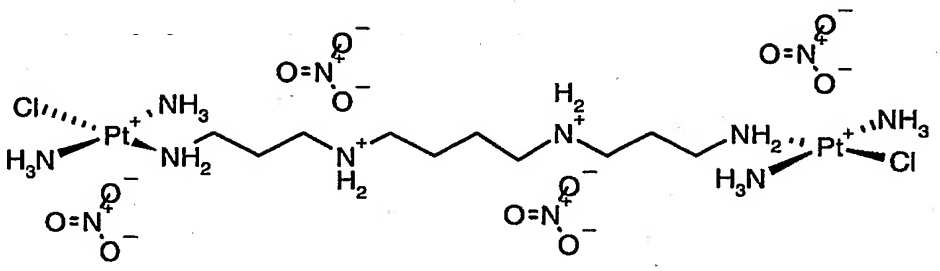
Formula II

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-6,11-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3 of formula III, described in Example 17, page 15, line 32-38 of US 6,022,892



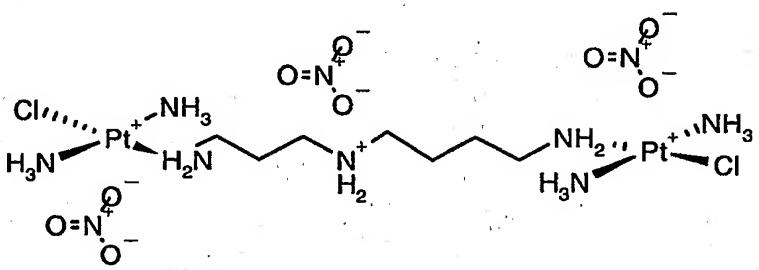
Formula III

bis{trans(diammine)(chloro)platinum(II)}-μ-(1,12-diamino-4,9-diazadodecane-N^1,N^{12}) dinitrate salt . 2HNO_3 of formula IV, described in Example 2 of US 6,596,889:



Formula IV

bis{trans(diammine)(chloro)platinum (II)}-μ-(1,8-diamino-4-azaoctane-N^1,N^8) dinitrate salt . HNO_3 of formula V, described in Example 1 of US 6,596,889:



Formula V

Solid Lipid Nanoparticle (SLN) formulations of platinum compounds can be obtained using solid lipids, surfactants and co-surfactants as excipients, using any of the methods disclosed in the above mentioned patent documents, which are herein incorporated by reference.

The nanoparticles of platinum compounds are obtained from warm microemulsions using the technology described (US 5,250,236). SLN are loaded with hydrophilic or hydrophobic platinum compounds which may be dissolved in the internal phase of the microemulsions. The platinum compounds-SLN are of spherical shape, with

average diameter between 70 and 200 nm, and are suitable to intravenous and oral administration.

Platinum compounds-SLN are absorbed through the lymph when administered by oral route. When administered intravenously, SLN are able to significantly alter the platinum compounds pharmacokinetics observed after administration of solution formulations. Moreover, SLN can enter into the tumor cells within a few minutes and are able to overcome physiological barriers (US 6,238,694, US 6,419,949).

Nanoparticles can be further elaborated to obtain stealth SLN, able to avoid reticular-endothelial system recognition (US 6,419,949).

Use of platinum compounds-SLN in anticancer therapy according to the invention provides the following advantages:

1. Improvement of oral bioavailability of poorly absorbed platinum compounds or of compounds unstable in the gut lumen;
2. Reduction of undesired interaction between the platinum compound and stomach/gut mucosa after oral administration, thus minimizing local toxicity;
3. Maximization of the oral bioavailability due to absorption of intact nanoparticles via the lymphatic system, with no hepatic first-pass effect;
4. Possibility to administer poorly water soluble platinum compounds by parenteral route;
5. Reduction of platinum compound-protein binding, and increase of the rate and extent of drug distribution;
6. Platinum compound protection from endogenous molecules in blood that may degrade/inactivate the compound before it gets to the tumor target;
7. Change of pharmacokinetic profile of platinum compounds given intravenously by slowing down the drug release from the formulation and thus decreasing the peak concentrations and increasing the residence time in the systemic circulation;

8. Therapeutic index improvement by targeting to the tumor cells (enhanced permeability and retention effect), and gradual delivery of platinum compounds inside the cells with better anticancer efficacy;
9. Modification of the drug distribution pattern, including passage of the blood-brain barrier.

The platinum compounds-SLN of the invention may be administered to patients affected by cancer usually responsive to platinum compounds, suitably formulated in pharmaceutical formulations for oral and intravenous administration. Guidelines for the appropriate dosage regimens may be found in the above mentioned US patents disclosing platinum compounds.

EXAMPLE

EXAMPLE 1

SLN of bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-7,10-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3

Bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-7,10-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3 of formula II (described in Example 17, page 15, line 25-31 of US 6,022,892) is a potent bisplatinum complex endowed with outstanding antitumor activity in a variety of tumor cell lines. Nanoparticles of this compound were prepared with the procedure above described (US 5,250,236) using deoiled lecithin, stearic acid, taurocholate, propionic acid, and an aqueous solution (0.01M NaCl, 0.01M HCl) of the bisplatinum complex. The warm microemulsion was dispersed in cold water (2 - 4 °C). Nanoparticles dispersion was repeatedly washed by dialfiltration (100,000 Da cut-off) with distilled water.

HPLC and ICP analyses of the obtained bisplatinum complex-SLN demonstrated that more than 90% of the loaded bisplatinum complex was incorporated into the nanoparticles. SLN mean diameter was 120 nm.

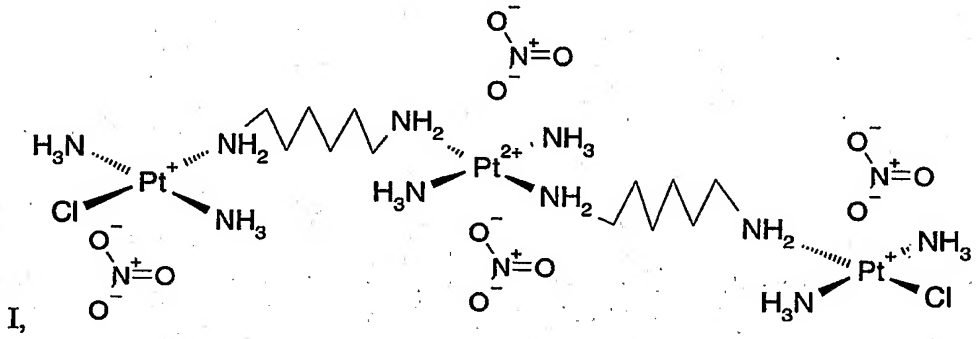
The platinum compound is stable in human plasma when incorporated in solid lipid nanoparticles and does not interact with plasma proteins. Bisplatinum complex-SLN is well tolerated when administered to CD1 mice and shows an improved therapeutic index when compared to aqueous solutions of the same compound.

CLAIMS

1. Solid Lipid Nanoparticles of platinum compounds.

2. Solid Lipid Nanoparticles according to claim 1 wherein the platinum compounds are platinum complexes.

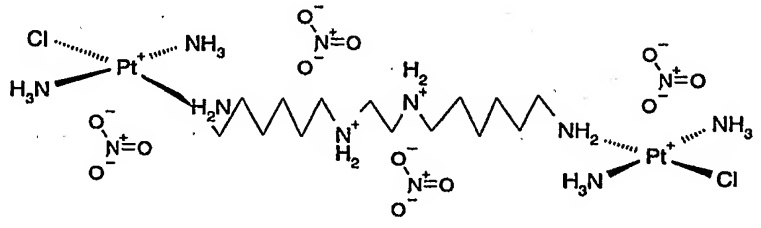
3. Solid Lipid Nanoparticles according to claim 2, wherein the platinum complex is selected from trans-{bis[trans(diammine)(chloro)platinum (II)(μ-1,6-hexanediamine)]}diammineplatinum tetranitrate salt of formula I



I,

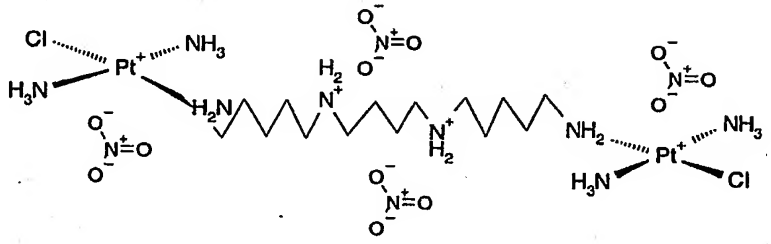
Formula 1

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-7,10-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3 of formula II,



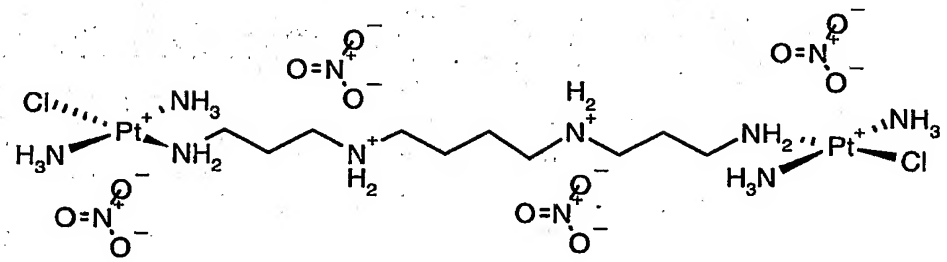
Formula II

bis{trans(diammine)(chloro)platinum(II)}μ-(1,16-diamino-6,11-diazahexadecane-N1,N16) dinitrate salt . 2 HNO_3 of formula III,



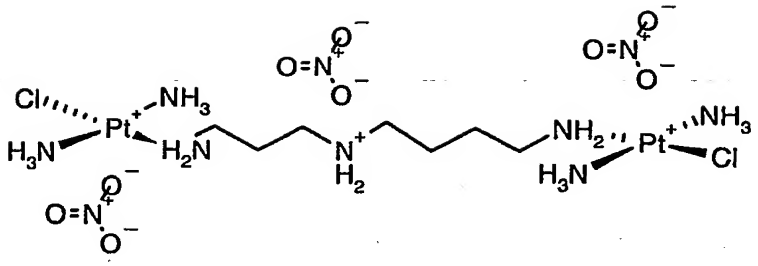
Formula III

bis{trans(diammine)(chloro)platinum(II)}-μ-(1,12-diamino-4,9-diazadodecane-N^1,N^{12}) dinitrate salt . 2HNO_3 of formula IV,



Formula IV

bis{trans(diammine)(chloro)platinum (II)}-μ-(1,8-diamino-4-azaoctane-N^1,N^8) dinitrate salt . HNO_3 of formula V,



Formula V

4. Pharmaceutical compositions comprising the solid lipid nanoparticles of claims 1-3.

5. A method of treating patients affected by cancer sensitive to platinum complexes which comprises administering to said patient a therapeutically effective amount of the solid lipid nanoparticles of claims 1-3.